b is 0 to 3; and

~~~~ indicates that the chirality of the carbon atom to which it is attached is either R or S;

wherein said surface comprises gold.

REMARKS

Claims 19-36, 41-44 and 49-58 stand rejected. Support for the amendments to the specification and to claims 19 and 41 can be found, for example, in the claims as originally filed. The misspelling "enantimomer" is corrected to enantiomer in the specification, including claims 1 and 9 as filed, and in pending claim 19. Claim 41 is amended from a dependent to an independent claim by incorporating subject matter from claim 1, from which it originally depended. This amendment is fully supported by the specification and does not incorporate new matter. Accordingly, after entry of this amendment, claims 19-36, 41-44 and 49-58 are pending in the instant application.

CLAIM REJECTIONS

1. Claims 19-36, 41-44 and 49-58 stand rejected under 35 U.S.C. § 103.

In the Office Action, the Examiner rejected claims 48-50 as anticipated under 35 USC § 103(a) by Mrksich et al.[1], reference A18 ("Mrksich") in view of Hodneland et al.[2], reference A7 ("Hodneland I"), Houseman et al.[3], reference A9 ("Houseman") and Sigal et al.[4], reference A25 ("Sigal") and, if necessary, further in view of Deng et al.[5], reference A3

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[1] Mrksich et al., "Using Self-Assembled Monolayers that Present Oligo(ethylene glycol) Groups to Control the Interactions of Proteins with Surfaces," *Am. Chem. Soc.*, 680, 361-373 (1997)

[2] Hodneland et al., "Biomolecular Surfaces that Release Ligands Under Electrochemical Control," *J. Am. Chem. Soc.*, 122, 4235-4236 (2000)

[3] Houseman et al, "The Role of Ligand Density in the Enzymatic Glycosylation of Carbohydrates Presented on Self-Assembled Monolayers of Alkanethiolates on Gold," *Agnew. Chem. Int. Ed.*, 38, 782-785 (1999)

[4] Sigal et al., "Effect of Surface Wettability on the Adsorption of Proteins and Detergents," *J. Am. Chem. Soc.*, 120, 3464-3473 (1998)

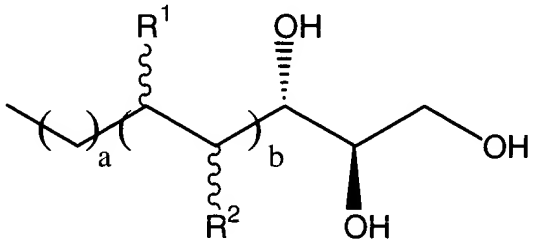
[5] Deng et al., "Self Assembled Monolayers of Alkanethiolate Presenting Tri(propylene sulfoxide) Groups Resist the Adsorption of Protein," *J. Am. Chem. Soc.* 118, 5136-5137 (1996)
~~~~

("Deng") or Hodneland et al.[6], reference A8 ("Hodneland II"). Specifically, the Office Action asserts in relevant part:

> [t]he claims are drawn to substrate containing alkanethiolate moieties of formula (5) or an alkanethiol moieties [sic.] of formula (1) on a surface of gold, and to chip containing the substrate and cells.
>
> Mrksich et al (A18) disclose using alkanethiol or alkanethiolate moieties on a surface of gold as a substrate for protein or cells.
>
> Hodneland et al (A7), Houseman et al (A9) and Sigal et al (A25), and if needed Deng et al (A3) or Hodneland et al (A8) disclose alkanethiol or alkanethiolate moieties having different groups for adhering protein or cells to a gold surface.
>
> It would have been obvious to select preferred groups for the alkanethiol or alkanethiolate moieties of Mrksich et al in view of the different groups disclosed by Hodneland et al (A7), Houseman et al (A9) and Sigal et al (A25), and if needed Deng et al (A3) or Hodneland et al (A8) contained by alkanethiol or alkanethiolate moieties. Office Action at 4.

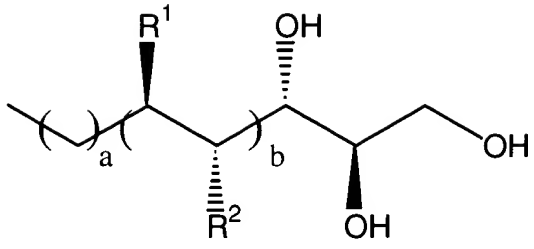
Applicant respectfully traverses this rejection. Neither Mrksich alone, nor Mrksich in combination with the other references cited in the Office Action, teaches or suggests self-assembled monolayers (SAMs) of the alkanethiolates of the present invention. Applicant respectfully submits that the claims as amended above are patentable over these references for at least the following reasons, and requests removal of these rejections.

The present invention Mrksich teaches, among other things, alkanethiol chains of the present invention, which are terminated with a "-T" moiety of formula (2) or formula (2') at one end, which are described in the specification as follows:



(2)

[6] Hodneland et al., "Design of Self-Assembled Monolayers That Release Attached Groups Using Electrical Potentials," *Langmuir* 13, 6001-6003 (1997)



(2')

R^1 and R^2 are each individually selected from the group consisting of H and OH;

a is 0 to 3;

b is 0 to 3; and

~~~~ indicates that the chirality of the carbon atom to which it is attached is either R or S.

(a) The Teachings of ***Mrksich*** *(A18) provide no teaching or guidance as to whether SAMs presenting terminal groups of the "-T" moiety of the present invention are capable of effective inhibition of protein binding.*

Mrksich does not teach or suggest the alkanethiol chains of the present invention, which are terminated with a "-T" moiety of formula (2) or formula (2') at one end. Mrksich teaches aklanethiolate SAMs bonded to a surface at one end, and terminated in an ethylene glycol (page 361), tri(propylene sulfoxide) (page 365) or benzensulfonamide group (page 365) on the other, as well as the resistance of these SAM-coated surfaces to protein adsorption. Mrksich at 361-365. Mrksich does not teach or suggest alkanethiol compounds of formula (1) or formula (5) that comprise the "-T" moiety at the end distal to the mercapto group in formula (1), or distal to the surface bond in formula (5). Instead, Mrksich teaches coating a surface with propylene sulfoxide terminal groups that inhibit protein binding to the coated surface. Mrksich at 365.

Mrksich recites that the inhibition of protein binding to SAM surfaces presenting propylene sulfoxide terminated surface-bound alkanethiol molecules "suggests that PEG is not unique in its ability to serve as an inert surface, but that there will probably be many such
~~~~

polymers." Mrksich at 365. However, Mrksich provides no teaching or guidance as to whether SAMs presenting terminal groups of the "-T" moiety of the present invention are capable of effective inhibition of protein binding. Instead, Mrksich teaches that SAMs of alkanethiolates on gold that present ethylene glycol groups distal to the points of surface attachment are "the standard choice for applications requiring inert surfaces" that resist protein binding, and that the ethylene-glycol terminated class of SAMs is "the best that is currently available" for studying the relationship between surface structure and interfacial properties such as protein binding. Mrksich at 361.

In contrast, the present invention teaches in relevant part that SAMs terminated in a "-T" moiety of formula (2) or formula (2'), such as a mannitol group of compound **1a** or **1b**, can be "substantially more effective" at inhibiting protein binding in localized surface areas than tri(ethylene glycol)-terminated alkanethiolate SAMs. Specification at 18-19. Accordingly, Mrksich teaches optimal inhibition of protein binding to an alkanethiolate SAM by presenting ethylene-glycol terminated groups, while Mrksich does not teach or suggest protein binding inhibition by presenting the "-T" moieties of the present invention, such as those of formula (2) and formula (2').

*(b) The Teachings of **Hodneland I** (A7) disclose SAMs to selectively bind and release a ligand such as biotin that are not structurally homologous to the "-T" terminal group presented in the present invention.*

Hodneland I teaches an alkanethiolate SAM presenting a quinone propionic ester. The quinone propionic ester can bind a biotin molecule and the bound biotin molecule is selectively released upon application of a reductive potential to the underlying gold surface (the reductive potential reduces quinone to hydroquinone, which undergoes lactonization to release biotin). Hodneland at 4236. Hodneland teaches that "it is essential that the monolayers remain inert to non-specific adsorption of protein both before and after release of the [biotin] ligand. Accordingly, the monolayers used here present the electroactive [quinone propionic ester] tether at low density (approximately 1% of total alkanethiolate) surrounded by tri(ethylene glycol) groups because the latter are highly effective at preventing non-specific

adsorption of protein." Hodneland at 4235.

Hodneland does not teach or suggest alkanethiolate SAMs comprising the "-T" terminal group of the present invention to inhibit protein binding to a SAM surface. First, the electroactive tether disclosed in Hodneland does not teach or suggest the compounds of the present invention because (a) it is primarily provided to selectively bind and release a ligand such as biotin and (b) it is not structurally homologous to the "-T" terminal group presented in the present invention. Second, apart form surface-bound molecular chains terminating the electroactive tether moiety, Hodneland teaches that it is "essential" that the remainder of the SAM surface remain inert to protein binding and teaches the use of "highly effective" tri(ethylene glycol) terminated chains for this purpose. Hodneland at 4235.

Likewise, if combined with Mrksich, neither Hodneland nor Mrksich teaches or suggests the inhibition of non-specific protein binding to a surface by presenting the "-T" moieties of the present invention. Nor is the use of alkanethiolate SAMs presenting the "-T" moieties of the present invention to inhibit nonspecific protein binding to the surface obvious in light of the combination of Mrksich and Hodneland because both references teach that optimal inhibition of non-specific protein binding is obtained by SAMs presenting ethylene glycol terminal moieties at the surface.

(c) *The Teachings of* ***Houseman (A9)*** *disclose the use of tri(ethylene glycol) terminal groups to resist nonspecific adsorption of protein to the SAM surface, to the exclusion of other possible terminal moieties.*

Housemen discloses mixed alkanethiolate SAMs presenting N-acetylglucosamine and tri(ethylene glycol) groups. Houseman teaches that "the tri(ethylene glycol) groups resist the nonspecific adsorption of protein to the model substrate." Houseman at 783.

Houseman does not teach or suggest alkanethiolate SAMs comprising the "-T" terminal group of the present invention to inhibit protein binding to a SAM surface. Houseman specifically teaches that one of the characteristics of SAMs that make them the "best available class of model substrates for studies in bio-interfacial science" is that they are "inert to the nonspecific adsorption of protein." Houseman at 784. Accordingly, Houseman

does not teach or suggest the use of compounds of the present invention to inhibit protein binding because: (a) Houseman only teaches the use of tri(ethylene glycol) terminal groups to resist nonspecific adsorption of protein to the SAM surface and (b) Houseman teaches that this inhibition of nonspecific protein surface adsorption is an important characteristic of the SAM surface.

Likewise, if combined with Mrksich, both references teach that optimal inhibition of non-specific protein binding is obtained by SAMs presenting ethylene glycol terminal moieties at the surface. Neither Houseman nor Mrksich teaches or suggests the inhibition of non-specific protein binding to a surface by presenting terminal moieties by the "-T" moieties of the present invention.

(d) The Teachings of ***Sigal*** *(A25) disclose the uniquely superior ability of SAMs terminated in hexa(ethylene glycol) groups to resist nonspecific adsorption of protein to the SAM surface.*

Sigal provides a study of the nonspecific adsorption of various proteins alkanethiolate SAMs presenting a variety of surface groups as a function of surface wettability. Sigal at 3464, 3466. Sigal teaches that SAMs presenting a hexa(ethylene glycol) moiety were "the single exception" to a more varied protein adsorption properties observed for other terminal moieties in that the SAMs presenting a hexa(ethylene glycol) group were "resistant to the adsorption of all the proteins [studied]." Sigal at 3472. However, Sigal does not disclose or suggest alkanethiolate SAMs comprising the "-T" terminal group of the present invention to inhibit protein binding to a SAM surface. Accordingly, Sigal does not teach or suggest the use of compounds of the present invention to inhibit protein binding because Sigal teaches the uniquely superior ability of SAMs terminated in hexa(ethylene glycol) groups to resist nonspecific adsorption of protein to the SAM surface.

Likewise, if combined with Mrksich, both references teach that optimal inhibition of non-specific protein binding is obtained by SAMs presenting ethylene glycol terminal moieties at the surface. Neither Sigal nor Mrksich teaches or suggests the inhibition of non-specific protein binding to a surface by presenting terminal moieties by the "-T" moieties of

the present invention.

(e) *The Teachings of* ***Deng (A3)*** *disclose aklanethiolate SAMs presenting tri(propylene sulfoxide) groups for the inhibition of nonspecific protein binding to the surface of alkanethiolate SAMS, which are not hydrogen bond donors.*

Deng does not teach or suggest the alkanethiol chains of the present invention, which can be terminated with a "-T" moiety of formula (2) or formula (2') at one end. Instead, Deng teaches aklanethiolate SAMs presenting tri(propylene sulfoxide) groups for the inhibition of nonspecific protein binding to the surface of alkanethiolate SAMs. Deng at 5136. Deng notes that SAMs presenting ethylene glycol moieties "effectively resist the nonspecific adsorption of protein" and tri(propylene sulfoxide) groups as an alternative terminal group to ethylene glycol for inhibition of nonspecific protein adsorption. Deng at 5136.

Not only does Deng not teach or suggest alkanethiol compounds of formula (1) or formula (5) that comprise the "-T" moiety, but the tri(propylene sulfoxide) groups of Deng are *not* hydrogen bond acceptors, while the compounds of the present invention can be hydrogen bond acceptors, for example at the –OH groups on the "-T" moiety. Specifically, Deng teaches that the sulfoxide group "was chosen by mimicking characteristics of the structurally unrelated oligo(ethylene glycol) group," (Deng at 5137) based in relevant part on the fact that both ethylene glycol and tri(propylene sulfoxide) contained structures that "are hydrogen bond acceptors *but not* donors" (Deng at 5136) (emphasis added).

Likewise, if combined with Mrksich, both references teach that optimal inhibition of non-specific protein binding is obtained by SAMs presenting ethylene glycol terminal moieties at the surface. Neither Deng nor Mrksich teaches or suggests the inhibition of non-specific protein binding to a surface by presenting terminal moieties by the "-T" moieties of the present invention, which are capable of being hydrogen bond acceptors or hydrogen bond donors.

(f) *The Teachings of* ***Hodneland II*** *(A8) describe an alkanethiolate chain presenting a catechol orthoformate group that acts as an electroactive tether that is primarily provided to design substrates that can release immobilized groups and which is not structurally homologous to the "-T" terminal group presented in the present invention.*

Hodneland II teaches an alkanethiolate SAM presenting a catechol orthoformate group. Hodneland II at 6001. The catechol orthoformate group can undergo an irreversible two-electron oxidation to produce an orthoquinone and release an orthoformate substituent upon application of a reductive potential to the underlying gold surface. Hodneland II at 6001. Hodneland teaches that "This work provides a methodology for the design of substrates that can release immobilized groups. The focus of this Letter is on the design and demonstration of an appropriate electrical reaction and on the characterization of a monolayer that incorporates this reactive group." Hodneland II at 6003.

Hodneland II does not teach or suggest alkanethiolate SAMs comprising the "-T" terminal group of the present invention to inhibit protein binding to a SAM surface. The electroactive tether disclosed in Hodneland II does not teach or suggest the compounds of the present invention because (a) it is primarily provided to design substrates that can *release* immobilized groups and (b) it is not structurally homologous to the "-T" terminal group presented in the present invention.

Likewise, if combined with Mrksich, neither Hodneland II nor Mrksich teaches or suggests the inhibition of non-specific protein binding to a surface by presenting the "-T" moieties of the present invention. Nor is the use of alkanethiolate SAMs presenting the "-T" moieties of the present invention to inhibit nonspecific protein binding to the surface obvious in light of the combination of Mrksich and Hodneland II because there is no suggestion to combine these references: Mrksich teaches that optimal inhibition of non-specific protein binding is obtained by SAMs presenting ethylene glycol terminal moieties at the surface, while Hodneland II is directed to the design of substrates that release immobilized moieties, for example upon application of a reductive potential to the substrate.

By teaching the importance of inhibition of nonspecific protein binding to SAM

surfaces, and not disclosing the compounds of the present invention, the combined teachings of Mrksich and Hodneland I, Houseman, Sigal, Deng and Hodneland II in no way teach or suggest the present invention, and only impermissible hindsight reconstruction of these references in light of the specification of the present invention allow one skilled in the art to practice the present invention. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

2. Claims 19-36, 41-44 and 49-58 stand rejected for obviousness-type double patenting.

The Office Action rejected claims 19-36, 41-44 and 49-58 as being unpatentable over claims 1-117 of copending U.S. Patent Application Ser. No. 09/923,760 or claims 1-41 of copending U.S. Patent Application Ser. No. 09/797,166. Specifically, the Office Action asserts in relevant part:

> Although the conflicting claims are not identical, they are not patentably distinct from each other because the presently claimed alkanethiolate moieties of formula (5) or an alkanethiol moieties [sic.] of formula (1) and their uses would have been obvious from the similar moieties of the claims of the copending applications. Office Action at 5.

Applicant respectfully traverses this rejection.

(a) *The obvious-type double patenting rejection is improper because it fails to make clear the differences between the instant invention and the claims of the co-pending applications, and the reasons why one skilled in the art would find those differences obvious.*

Applicant respectfully asserts that this rejection is improper because it fails to make clear:

> (A) the differences between the inventions defined by the allegedly conflicting claims – a claim in the patent compared to a claim in the application; and (B) the reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim in issue is an obvious variation of the invention defined in a claim in the patent. M.P.E.P. § 804, Subsection (II)(B)(1).

That is, the Office Action fails to assert any basis in the art for the conclusion that the moieties

of formula (5) or formula (1) of the present invention, and their uses, are either (a) similar to or (b) obvious over the inventions claimed in the recited copending applications. Applicant can find no assertion in the Office Action of differences (for example, differences of chemical structure or function) that are allegedly "not patentably distinct" between the structural formulas recited in the copending applications at issue in this rejection and structures recited by the claims of the present invention. Furthermore, Applicant can find no assertion in the Office Action of reasons why one skilled in the art would find structures recited in the copending applications and the instant invention to be "obvious from similar moieties." Applicant respectfully requests that this rejection be withdrawn.

(b) *The claims of the instant invention are not obvious over the claims of co-pending U.S. Patent Application Nos. 09/797,166 and 09/923,760.*

Alternatively, Applicant traverses this rejection because neither claims 1-41 of copending application 09/797,166 nor claims 1-177 of co-pending application 09/923,760 are obvious over the allegedly similar chemical structures recited in the claims of the present invention.

(i) *The claims of 09/797,**166** do not recite a "-T-" moiety comprising a 1,2,3-trihydroxyl-alkyl group situated at the terminal end of an alkanethiol or alkanethiolate moiety.*

The 09/797,166 ("'166 application") patent application includes new alkanethiols and disulfides, and SAMs prepared from these compounds that can release an attached leaving group, for example upon a "trigger" of electrical or chemical reduction. *E.g.*, '166 patent application at page 9. lines 2-8. Specifically, the claims of the '166 patent application recite (a) alkanethiols according to a "formula (1)" (i.e., "HS-L-Q^1-T-Q^2-M-G-Z") recited in claim 1; disulfides according to a "formula (5)" (i.e., "J-S-S-L- Q^1-T-Q^2-M-G-Z") recited in claim 9; and surface-bound alkanethiolate moieties according to a "formula (8)" (i.e., Surf-S-L- Q^1-T-Q^2-M-G-Z") recited in claim 18. '166 patent application at 36-39, 40-43 and 44-47. The remaining claims of the '166 patent are dependent on these three claims and thereby incorporate at least one of these structural formulae. 35 U.S.C. § 112, ¶4 (2002); 37 C.F.R. §

1.75(c); M.P.E.P. 608.01(i) (Dependent claims include all the limitations of the claims on which they depend). The chemical structures corresponding to each lettered moiety are recited in the claims of the '166 application, and are not reproduced herein.

None of the formulae recited in the claims of the '166 patent application comprise a terminal group corresponding to formula (2) or formula (2') of the present invention. The "-T" group of the '166 application is attached to a "Q^2" group in all the formulae recited in the claims of the '166 application. Specifically, the "-T-" group in the '166 application includes a 1-oxo, 2,3-dihydroxyl-alkyl group, wherein the "-T-" moiety is bonded to the Q^2 group at the 1-oxo position. '166 application at page 37, line 4. In contrast, the present application teaches a "-T-" moiety comprising a 1,2,3-trihydroxyl-alkyl group wherein the "-T-" moiety forms the terminal end of the formula distal to the HS- moiety of the alkanethiol of formula (1) or the Surface-Sulfur bond in formula (5). Accordingly, the compounds recited in the '166 application are patentably distinct from the present invention because they do not recite a "-T-" moiety comprising a 1,2,3-trihydroxyl-alkyl group situated at the terminal end of an alkanethiol or alkanethiolate moiety.

Nor do the teachings of the '166 application or the prior art suggest that compounds of the *instant application* (i.e. alkanethiolate SAMs presenting the terminal "-T" moiety) would effectively inhibit the nonspecific protein binding to alkanethiolate SAMs. First, the '166 application teaches the use of alkanethiolate SAMs presenting tri(ethylene glycol) groups as a means of ensuring a surface is "highly effective at preventing non-specific adsorption of protein." '166 application at page 28, lines 10-14. Second, the prior art references cited by the Office Action teach that protein binding to alkanethiolate SAMs is dependent on the terminal moieties presented distal to the surface binding site. For example, Sigal presents a study of the binding of various proteins to alkanethiolate SAMs with different terminal moieties and teaches that the "character of the surface can be controlled by using linear alkanethiols terminated with [different] functional groups." Sigal at 3465. Specifically, Sigal teaches a variety of protein and detergent binding that was dependent on the surface moiety structure presented. Sigal at 3466. The alkanethiolate SAMs of the '166 application present a terminal "-Z" leaving group such as biotin or the tripeptide RGD. '166 application at pages 28-29, 33-

35. If the leaving group is removed from the SAMs of the '166 application, the SAMs will present a benzoquinone-based "-G" moiety to unbound proteins. In contrast, the present invention teaches presentation of a "-T" group comprising hydroxyl groups to unbound proteins.

One skilled in the art would read Signal to suggest that, because of the lack of homology between the "-T" group of the present invention and the "-G" or "-Z" moieties of the '166 application, even if the "-G" or "-Z" moieties effectively inhibit protein binding, it would not be obvious that an alkanethiolate SAM terminated in a "-T" group according to the present invention would have the capability of effectively inhibiting protein binding to the SAM.

(ii) *The claims of 09/923,**760** do not suggest that compounds of the instant application would effectively inhibit the nonspecific protein binding to alkanethiolate SAMs.*

The 09/923,760 patent application ("'760 application") claims recite alkanethiols, disulfides alkanethiolate moieties, and SAMs prepared from these compounds. The SAMs of the '760 application can immobilize certain proteins at the surface of the SAM, for example upon binding of a fusion protein to a "reactant ligand" at the end of an alkanethiolate SAM chain distal to the attachment to the chain to the surface. *E.g.,* '760 patent application at page 13, lines 6-22. Specifically, the claims of the '760 patent application recite alkanethiols according to a "formula (I)" (i.e., "HS—L-Q-T") recited in claim 1; disulfides according to a "formula (V)" (i.e., "J-S-S-L-Q-T") recited in claim 8; surface-bound alkanethiolate moieties according to a "formula (VII)" (i.e., "Surf-S-L-Q-T") recited in claim 16; moieties according to a "formula (VIII)" (i.e., "-Q-T") recited in claim 28; moieties according to a "formula (IX)" (i.e., "-L-Q-T") recited in claim 32; alkanethiolate moieties according to a "formula (X)" (i.e., "Surf-S-L-Q-Z") recited in claim 37; moieties according to a "formula (XI)" (i.e., "-Q-Z") recited in claim 38; moieties according to a "formula (XII)" (i.e., "-L-Q-Z") recited in claim 39; and alkanethiolate moieties according to a "formula (XIII)" (i.e., "-S-L-Q-T") recited in claim 95. '760 application at 89-114. The chemical structures corresponding to each lettered moiety are recited in the claims of the '760 application, and are not reproduced herein. The remaining claims of the '760 patent incorporate at least one of these structural formulae. 35

U.S.C. § 112, ¶4 (2002); 37 C.F.R. § 1.75(c); M.P.E.P. 608.01(i) (Dependent claims include all the limitations of the claims on which they depend). Accordingly, the alkanethiolate SAMs of the '760 application present terminal groups that are either a "-T" moiety reactant ligands or "Z" reaction products.

The "-T" group in the '760 application is a "reactant ligand" which the specification defines as "a ligand which binds a polypeptide and forms a covalent bond between the ligand and the polypeptide." '760 specification at page 13, lines 23-24. Reactant ligands are recited in formula (II), formula (III), formula (IV) (e.g., as in claims 13-15). The '760 application does not teach a structure of formula (2) or formula (2') for the "-T" group of the *present* invention. Furthermore, even if the moieties of formulae (II), (III) and (IV) of the '760 application provided the protein binding inhibition properties of the "-T" groups of the present invention, the difference in structure between the compounds of the reactant ligands disclosed in the '760 application and the "-T" groups of the present invention, provide no teaching or suggestion to one skilled in the art of a similar protein binding inhibition functionality among the two groups of compounds. The structures of alkanethiolate SAMs presenting a "-Z" reactant product in the '760 application are readily understood from the specification to be the reactant ligand bound, for example, to a fusion polypeptide. So, the terminal "-Z" moiety also does not teach a structure of formula (2) or formula (2') for the "-T" group of the *present* invention.

As with the '166 application, the '760 application does not suggest that compounds of the *instant application* would effectively inhibit the nonspecific protein binding to alkanethiolate SAMs. As discussed above, the prior art teaches one skilled in the art that because of the lack of homology between the "-T" group of the present invention and the "-T" or "-Z" moieties of the '760 application, that even if the "-T" or "-Z" moieties of the '760 application effectively inhibit protein binding, it would not be obvious that an alkanethiolate SAM terminated in a "-T" group according to the *present* invention would have the capability of effectively inhibiting protein binding to the SAM.

Accordingly, Applicant respectfully requests that this rejection be withdrawn.

3. Claims 19-36, 41-44 and 49-58 stand rejected under 35 U.S.C. § 112, first paragraph.

The Office Action rejected claims 19-36, 41-44 and 49-58 under 35 USC § 112, first paragraph, alleging that the specification fails to enable one skilled in the art to practice the full scope of these claims. Specifically, the Office Action asserts that:

> [c]laims 19-36, 41-44 and 49-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for formula (1) and (5), does not reasonably provide enablement for enantimomers [sic.] of the formula. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.
>
> The specification fails to disclose an enabling procedure for making specific enantimomers [sic.] of the formula. Office Action at 2.

Applicant respectfully asserts that this rejection is improper because synthetic methods for the specific enantiomers claimed are taught by the specification when read by one of ordinary skill in the art.

(i) *The specification teaches one of ordinary skill in the art which enantiomers are within the scope of formula (1) and formula (5).*

Applicant respectfully requests that the rejection of claims 19-36, 41-44 and 49-58 and 53-58 should be withdrawn because the specification as read by one of ordinary skill in the art provides adequate teaching of the synthesis of the compounds claimed.

The specification clearly teaches one of ordinary skill in the art which enantiomers are within the scope of formula (1) and formula (5). The compounds of formula (1) and formula (5) only possess stereogenic centers in their "-T" moiety, and the chirality of these centers is designated by bonds, as indicated by the bonds between the carbon and the 1-, 2- and 3-hydroxyl groups, or as a mixture of chiralities indicated by the "wavy" lines in part of formula (2). Specification at page 8, lines 1-21. One skilled in the art would understand that the recitation of "and the enantiomers" in the claims of the instant invention refer to the non-superimposable mirror images the compounds of the corresponding recited formula(e).

A specification meets the enablement requirement when it teaches one skilled in the

art to make and use the invention claimed without undue experimentation. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988); M.P.E.P. § 2164.01. A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). M.P.E.P. § 2164.08.

(ii) *The specification enables claims reciting compounds comprising the moieties of formula (1) and formula (5).*

Furthermore, the rejection of claims 19-21, 30-31, 41-42 and 49-52 should be withdrawn because these claims are drawn to compounds of formula (1) and formula (5) that the Office Action concedes are enabled by the instant specification. The specification teaches that the carbon atoms at the carbon-R^1 and carbon-R^2 bonds (designated by "wavy" lines) of the "-T" moiety in formula (1) of claim 41 as amended herein, and formula (5) of claim 19, "may be either R or S." Specification at 8 (lines 4-5). The Office Action acknowledges that formula (1) and formula (5) are enabled, but alleges that the specification fails to provide enablement for "specific" enantiomers of compounds of formula (1) and formula (5). Office Action at 2. In other words, since the compounds of formula (1) and formula (5) are enabled, compounds that possess the specified chirality at the carbon stereogenic centers of the 1-, 2- and 3-hydroxylalkyl groups of the "-T" moiety of both these formulae are enabled by the specification. Accordingly, Applicant further asserts that the enantiomers of these chiral configurations recited in formula (1) and formula (5) are *also* enabled by the specification.

Applicant asserts that the synthesis of enantiomers of the compounds of formula (1) and formula (5) are within the skill of the art. Both formula (1) and formula (5) recite "-T" moieties of formula (2), while certain dependent claims thereof recite "-T" moieties of formula (2'). Enantiomers of compounds of formula (1) or formula (5) are compounds with "-T" moieties that are the nonsuperimposible mirror image of the compounds of formula (2).

The specification supports the synthesis of compounds comprising "-T" moieties of formula (2). For example, the specification teaches the synthesis of alkanethiol chains comprising a mannitol terminal group, for example as compounds 1a and 1b at page 15.

The synthesis of the mannitol moiety, and the synthesis of an enantiomer thereof, are well known in the art. For example, synthesis of both the L and D forms of mannitol can be accomplished by reducing the corresponding mannose, as taught by Per J. Garegg et al.[7] (copy attached) and by Mark Andrews et al.[8] (copy attached). Mannitol moieties can also be synthesized in unnatural sugar forms, for example, as taught by Sharpless et al.[9] (copy attached). Other, more recent synthesis are taught by Wei et. al.[10] (copy attached), or Takahashi et al.[11] (copy attached).

Accordingly, enantiomers of compounds of formula (1) or formula (5) could be synthesized by a variety of stereospecific synthetic methods, including the use of a precursor molecule possessing the requisite chirality at the carbons at the 1-, 2- and 3- hydroxylalkyl positions for enantiomers of formula (2). The remaining dependent claims that recite formula (1) and formula (5) are also enabled because dependent claims include all the limitations of the claims on which they depend. 35 U.S.C. § 112, ¶ 4 (2002); 37 C.F.R. § 1.75(c); M.P.E.P. 608.01(i).

(iii) *The specification enables claims reciting compounds comprising the moiety of formula (2').*

Regarding the compounds comprising formula (2') recited in claims 22-28, 32-35, 43-44 and 53-56, the specification enables the synthesis of compounds of formula (1) and formula (5) comprising a "-T" moiety with the stereochemistry specified in formula (2') at carbon atoms bonded to the $-R^1$ and $-R^2$ groups, for example as recited in claims 22 and 43,

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[7] Per J. Garegg et al. "Hydrolysis of glycosides under reducing conditions," *Carbohydrate Res.* 1988, 176, 145-148

[8] Mark Andrews et al., "Selective hydrocracking of monosaccharide carbon-carbon single bonds under mild conditions. Ruthenium hydride-catalyzed formation of glycols," *J. Am. Chem. Soc.*, 1989, 111, 4131-4133

[9] Sharpless et al., "Total Synthesis of the L-Hexoses," *Science*, 1983, 220, 949-951

[10] Wei et. al. in "Synthesis of L-Sugars from 4-Deoxypentenosides," *Org. Lett.*, 2002, 4, 2281-2283

[11] Takahashi et al., "A Novel and Practical Synthesis of L-Hexoses from D-Glycono-1,5-lactones," *J. Am. Chem. Soc.* 2000, 122, 2995-3000

without undue experimentation. The specification teaches methods of synthesizing the alkanethiols and disulfides of the present invention. *E.g.*, Specification at 9-10. For example, the reaction scheme recited at page 9, line 12 ("9:12") of the specification can be adapted to synthesize various compounds of the present invention, for example as discussed from 9:13 – 10:27. Accordingly, compounds according to formula (1) (e.g., 9:13-10:8) or formula (5) (e.g., 10:9-10:27) can be produced possessing specific stereochemistry, for example as recited in claims 22 and 43. Furthermore, the specification provides a detailed example at page 15 of the synthesis of a compound with certain stereochemistry in the "-T" moiety at each of the carbon atoms bonded to R^1 and R^2, as recited in claims 22 and 43. Specifically, this portion of the specification teaches a reaction scheme employing a starting material (alkanethiols 1a or 1b) (Specification at 15:1-6), which are preserved by adding protecting groups prior to reaction with NaH/DMF in reaction step (a) (Specification at 15:11), and later removed by reaction with HCl/methanol in reaction step (c) (Specification at 15:13). This example on page 15 of the specification demonstrates one of stereosynthetic methods known in the art for producing a product with a desired stereochemistry at one or more carbon chiral centers, for instance by using a given enantiomer as a reactant and using a protecting group. See, e.g., M. Smith and J. March, "Advanced Organic Chemistry" (Wiley & Sons, 5th ed. 2001) at 166-167 (copy attached). Accordingly, enantiomers of compounds of formula (2') could be synthesized by a variety of stereospecific synthetic methods, including the use of a precursor molecule possessing the requisite chirality at the carbons at the 1-, 2-, 3-, 4- and 5-hydroxylalkyl positions of the "-T" group. The remaining dependent claims that recite formula (1) and formula (5) are also enabled because dependent claims include all the limitations of the claims on which they depend. 35 U.S.C. § 112, ¶ 4 (2002); 37 C.F.R. § 1.75(c); M.P.E.P. 608.01(i).

(iv) *The specification enables claims reciting compounds comprising various alkanethiolate moieties.*

Claims 29, 36 and 57-58 recite a substrate comprising "alkanethiolate moieties." The specification defines "alkanethiolate," for example at page 6, lines 7-8, and teaches a variety

of alkanethiolate moieties, for example as shown in formula (5) at page 10, lines 9-27. Methods for synthesizing alkanethiolate moieties, such as from alkanethiol molecules of formula (1), are also taught by the specification, for example at pages 9-10 and pages 14-16. The specification teaches the synthesis of various surfaces comprising alkanethiolate moieties (e.g., pages 10-13), including cell chips (e.g., pages 11-12) and protein chips (e.g., pages 12-13), and provides a series of non-limiting examples such as the synthesis of alkanethiol compounds (pages 15-16) and preparation and characterization of alkanethiolate-coated surfaces (e.g., pages 16-18). For example, the specification teaches the synthesis of alkanethiolate moieties from alkanethiol molecules such as **1a** and **1b** that comprise a mannitol group with stereochemistry analogous to the moiety of formula (2'). Specification at pages 15-16. Similar techniques are known in the art to form other alkanethiolate moieties, for example as taught by Garegg et al.[12], Mark Andrews et al.[13], Sharpless et al.[14], Wei et. al.[15], or Takahashi et al.[16] (copies attached).

Accordingly, the specification provides ample teaching of the preparation and use of a variety of surface-bound alkanethiolate moieties such that one skilled in the art would be able to prepare such moieties with specified stereochemistry as needed for any embodiment of the invention.

Accordingly, one skilled in the art would be able to make and use the claimed compounds, surfaces and methods of the invention, for example as recited in claims 19-36, 41-44 and 49-58, without undue experimentation. Applicant respectfully requests that this rejection be withdrawn.

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[12] Per J. Garegg et al. "Hydrolysis of glycosides under reducing conditions," *Carbohydrate Res.* 1988, 176, 145-148

[13] Mark Andrews et al., "Selective hydrocracking of monosaccharide carbon-carbon single bonds under mild conditions. Ruthenium hydride-catalyzed formation of glycols," *J. Am. Chem. Soc.*, 1989, 111, 4131-4133

[14] Sharpless et al., "Total Synthesis of the L-Hexoses," *Science*, 1983, 220, 949-951

[15] Wei et. al. in "Synthesis of L-Sugars from 4-Deoxypentenosides," *Org. Lett.*, 2002, 4, 2281-2283

[16] Takahashi et al., "A Novel and Practical Synthesis of L-Hexoses from D-Glycono-1,5-lactones," *J. Am. Chem. Soc.* 2000, 122, 2995-3000

4. Claims 19-36, 41-44 and 49-58 stand rejected under 35 U.S.C. § 112, second paragraph.

The Office Action rejected claims 19-36, 41-44 and 49-58 under 35 USC § 112, second paragraph as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Specifically, the Office Action asserts that:

> [c]laims 19-36, 41-44 and 49-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
>
> The meaning and scope of "enantimomers" is uncertain. It would be uncertain as to compounds that are enantimomers of formula (1) and (5).
>
> In formula (5) of claim 19, "Surf" has not been defined.
>
> Claims 41-44 are unclear by being dependent on a nonelected claim. Office Action at 3.

The spelling of "enantimomers" has been corrected to "enantiomers." The compounds recited in claim 1 have been incorporated into claim 41, to more clearly define the invention.

Formula (1) comprises a mercapto group (HS-) bonded to an "-L-" moiety at one end, while formula (5) comprises a bond between an "-L-" moiety and a surface at the comparable end. One skilled in the art would recognize that neither the mercapto-L bond in formula (1), nor the Surf-L bond in formula (5), creates a chiral center at the $-C(R_AR_A')-$ carbon atom to which the sulfur atom in formula (1), or the surface binding site in formula (5), are bound. *E.g.,* Specification at page 7, lines 10-15 and page 10, lines 15-20.

Both formula (1) and formula (5) comprise a sulfur atom bonded to an "-L-" moiety, which moiety is bonded to a "-Q-" moiety, which Q moiety is bonded to a "-T" moiety. Specification at page 7, line 11 and page 8, line 9. The specification recites a variety of functional groups for the "-L-," "-Q-" and "-T-" moieties that can be present in compounds of formula (1) or formula (5). *E.g.,* Specification at page 7, line 8 – page 9, line 5 and page 10, lines 15-20. One skilled in the art can recognize that the functional groups of the "-Q-" group do not provide chiral centers because each pair of bonds to the oxygen, nitrogen and carbon atoms of the structures recited do not form chiral centers. Specification at page 7, lines 21-24.

On the other hand, the "-T" moiety of formula (2) and formula (2') has two carbon atoms bonded to alcohol groups with a defined stereochemistry, and up to three pairs of stereocenters at the carbon atoms bonded to the R^1 and R^2 groups. Specification at page 8, lines 1-5 and page 10, lines 15-18. In formula (2), the carbon- R^1 and carbon- R^2 bonds are represented by a wavy line indicating that the chirality of the carbon atoms may be either R or S. Specification at page 8, lines 1-5. In formula (2'), the chirality of the carbon- R^1 and carbon- R^2 bonds are specified by the wedge nomenclature known in the art (the chirality depends on whether an -H or -OH group is substituted for R^1 and R^2). Specification at page 8, lines 20-22. Thus, only the "-T" moiety of both formula (1) and formula (5) possesses chiral center, and the exact orientation of the carbon atoms is taught, either as a fixed chirality or as a racemic mixture. Accordingly, the scope of the claim feature "and enantiomers of the alkanethiolate moieties" in pending independent claims 19 and 41, as well as the claims dependent therefrom, is clearly taught by the instant specification.

The recitation of "Surf" in formula (5) of claim 19 is defined in the specification, for example, by the recitation "Surf designates where the moiety attaches to the surface" at page 4, lines 1-2. The specification also discusses the meaning of "surface," for example by noting:

> Surf designates where the moiety attaches to the surface. The density of moieties on the surface is typically $10^{10} \pm 5\%$ per square centimeter. The moieties of the present invention may cover the entire surface, or may be patterned on the surface. Patterning may be carried out by, for example, by microprinting, as described in Mrksich, M.; Dike, L. E.; Tien, J.; Ingber, D. E.; Whitesides, G. M., *Experimental Cell Research* **1997** *235*, 305-313; Chen, C. S.; Mrksich, M.; Huang, S.; Whitesides, G. M.; Ingber, D. E., *Science* **1997**, *276*, 1425-1428; and Mrksich, M.; Whitesides, G. M., *TIBTECH.* **1995**, *13*, 228-235.
>
> Preferably the surface contains gold, more preferably the surface contains 50 to 100 atom percent gold. Preferably, the surface is pure or fine gold, or an alloy of gold with copper, silver, or a combination thereof.
>
> The surface may be on a base. The base may have the same composition as the surface (for example a gold surface on a gold plate), or the surface may be, for example, a film, foil, sheet, or plate, on a base having a different composition. The base may be any material, such as metal, ceramic, plastic, or a natural material such as wood.

Examples of bases include glass, quartz, silicon, transparent plastic, aluminum, carbon, polyethylene and polypropylene.

The surface material may be attached to the base by any of a variety of methods. For example, a film of the surface material may be applied to the base by sputtering or evaporation. If the surface material is a foil or sheet, in could be attached with an adhesive. Furthermore, the surface need not completely cover the base, but may cover only a portion of the base, or may form a pattern on the base. For example, portions of the base could be patterned by sputtering the base, covering those portions of the base where no surface material is desired. These patterns may include an array of regions containing, or missing, the surface material. Specification at page 10, line 19- page 11, line 14.

Accordingly, from the perspective of one of ordinary skill in the art, the recitation of "Surf" is defined in the specification. Applicant respectfully requests that this rejection be withdrawn.

CONCLUSION

In light of the arguments presented above, Applicant respectfully requests that this rejection be withdrawn.

Applicants respectfully assert that the claimed invention is not anticipated or obvious over the cited references, alone or in combination, and that the specification and claims comply with the requirements of 35 U.S.C. § 112. Accordingly, these rejections should be withdrawn and the pending claims allowed.

Should the Examiner feel that an interview may expedite the resolution of these matters or other formalities, he is kindly requested to contact the undersigned attorney.

Respectfully submitted,

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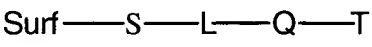
Appendix: Complete Pending Claims showing amendments

19. (Amended) A substrate, comprising:

(i) a surface layer comprising gold, and

(ii) a plurality of moieties, on at least a portion of said surface layer,

wherein said moieties are alkanethiolate moieties of formula (5) and [enantimomers]<u>enantiomers</u> of the alkanethiolate moieties of formula (5):



Surf——S——L——Q——T (5);

-L- is $-(A_x-B_y-E_z-D)_w-$;

each A, B, E and D are individually $C(R_AR_A')$-, $-C(R_BR_B')$-, $-C(R_ER_E')$-,and $-C(R_DR_D')$-, respectively;

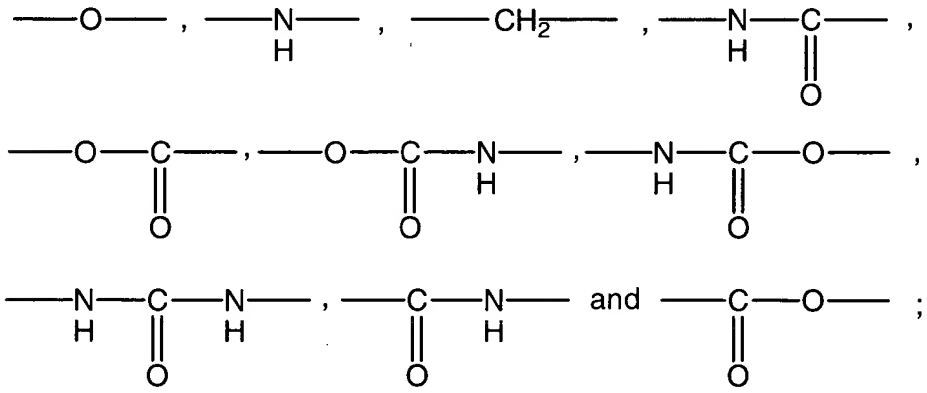
each R_A, R_B, R_E and R_D are individually H, or any two of R_A, R_B, R_E and R_D together form a bond, or R_A, R_B, R_E and R_D together with the atoms to which they are bonded form a six-membered aromatic ring;

each R_A', R_B', R_E' and R_D' are individually H, or any two of R_A', R_B', R_E' and R_D' together form a bond, or R_A', R_B', R_E' and R_D' together with the atoms to which they are bonded form a six-membered aromatic ring;

each x, y and z are individually either 0 or 1;

w is 1 to 5;

-Q- is selected from the group consisting of

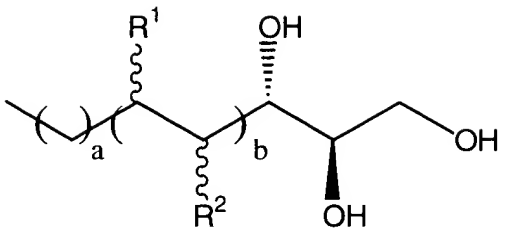


——O——, ——N(H)——, ——CH_2——, ——N(H)——C(=O)——,

——O——C(=O)——, ——O——C(=O)——N(H)——, ——N(H)——C(=O)——O——,

——N(H)——C(=O)——N(H)——, ——C(=O)——N(H)—— and ——C(=O)——O——;

-T is a moiety of formula (2)



(2);

R^1 and R^2 are each individually selected from the group consisting of H and OH;

a is 0 to 3;

b is 0 to 3;

~~~ indicates that the chirality of the carbon atom to which it is attached is either R or S; and

Surf designates where the moiety attaches to said surface.

20. The substrate of claim 19, further comprising:

(iii) a monolayer comprising said moieties,

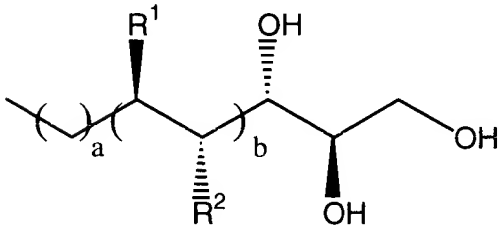
wherein said monolayer does not fail a cell patterning test at 12 days.

21. The substrate of claim 19, further comprising:

(iv) a base,

wherein said surface layer is on said base.

22. The substrate of claim 21, wherein -T is a moiety of formula (2')



(2').

23. The substrate of claim 22, wherein a is 1, b is 1 and at least one of R^1 and R^2 is OH.
~~~

24. The substrate of claim 22, wherein -L- contains 8 to 18 carbon atoms.

25. The substrate of claim 24, wherein -L- contains 1 or 0 double bonds, or 1 triple bond.

26. The substrate of claim 22, wherein -L- is an alkylene containing 6 to 18 carbon atoms.

27. The substrate of claim 22, wherein -Q- is -O- or $-CH_2-$.

28. The substrate of claim 23, wherein -L- is an alkylene containing 6 to 18 carbon atoms, and -Q- is -O-.

29. A substrate, comprising:

(i) a surface layer comprising gold, and

(ii) a monolayer comprising moieties, on at least a portion of said surface layer,

wherein said moieties are alkanethiolate moieties; and

said monolayer does not fail a cell patterning test at 12 days.

30. A cell chip, comprising:

(A) the substrate of claim 19, and

(B) cells, on said substrate.

31. A cell chip, comprising:

(A) the substrate of claim 20, and

(B) cells, on said substrate.

32. A cell chip, comprising:

(A) the substrate of claim 22, and

(B) cells, on said substrate.

33. A cell chip, comprising:

(A) the substrate of claim 24, and

(B) cells, on said substrate.

34. A cell chip, comprising:

(A) the substrate of claim 26, and

(B) cells, on said substrate.

35. A cell chip, comprising:

(A) the substrate of claim 28, and

(B) cells, on said substrate.

36. A cell chip, comprising:

(A) the substrate of claim 29, and

(B) cells, on said substrate.

41. (Amended) A method of making a substrate, comprising contacting a surface with [the anlakethiol of claim 1]an alkanethiol of formula (1) and the enantimomers of the alkanethiol of formula (1):

HS——L——Q——T (1),

wherein -L- is $-(A_x-B_y-E_z-D)_w-$;

each A, B, E and D are individually $C(R_AR_A')-$, $-C(R_BR_B')-$, $-C(R_ER_E')-$,and $-C(R_DR_D')-$, respectively;

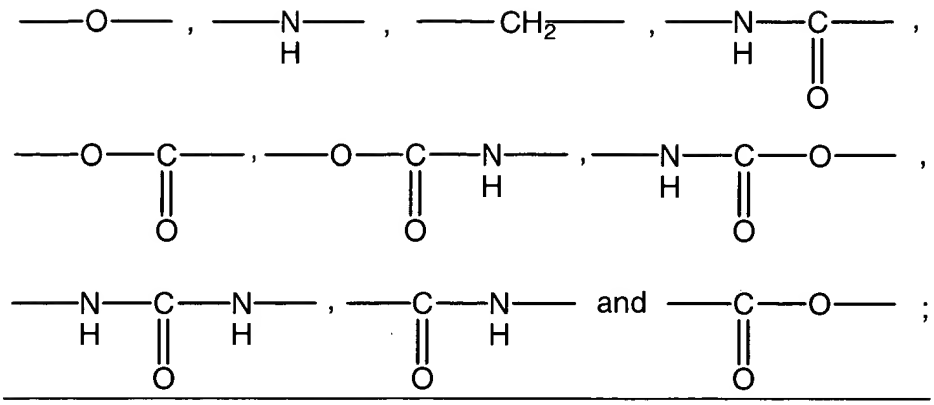
each R_A, R_B, R_E and R_D are individually H, or any two of R_A, R_B, R_E and R_D together form a bond, or R_A, R_B, R_E and R_D together with the atoms to which they are bonded form a six-membered aromatic ring;

each R_A', R_B', R_E' and R_D' are individually H, or any two of R_A', R_B', R_E' and R_D' together form a bond, or R_A', R_B', R_E' and R_D' together with the atoms to which they are bonded form a six-membered aromatic ring;

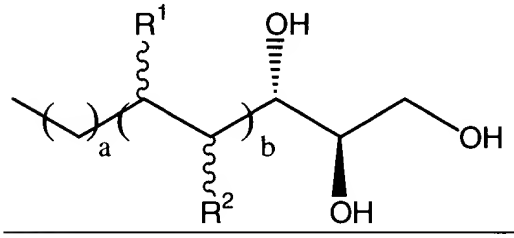
each x, y and z are individually either 0 or 1;

w is 1 to 5;

-Q- is selected from the group consisting of



-T is a moiety of formula (2)



(2);

R^1 and R^2 are each individually selected from the group consisting of H and OH;

a is 0 to 3;

b is 0 to 3; and

~~~~ indicates that the chirality of the carbon atom to which it is attached is either R or S;

wherein said surface comprises gold.

42. A method of making a substrate, comprising contacting a surface with the alkanethiol of claim 1;

wherein said surface comprises gold.

43. A method of making a substrate, comprising contacting a surface with the alkanethiol of claim 2;

wherein said surface comprises gold.
~~~~

44. A method of making a substrate, comprising contacting a surface with the alkanethiol of claim 8;

wherein said surface comprises gold.

49. A method of making a cell chip, comprising:

contacting cells with the substrate of claim 19.

50. The method of claim 49, further comprising allowing said cells to proliferate.

51. A method of making a cell chip, comprising:

contacting cells with the substrate of claim 20.

52. The method of claim 51, further comprising allowing said cells to proliferate.

53. A method of making a cell chip, comprising:

contacting cells with the substrate of claim 22.

54. The method of claim 53, further comprising allowing said cells to proliferate.

55. A method of making a cell chip, comprising:

contacting cells with the substrate of claim 28.

56. The method of claim 55, further comprising allowing said cells to proliferate.

57. A method of making a cell chip, comprising:

contacting cells with the substrate of claim 29.

58. The method of claim 57, further comprising allowing said cells to proliferate.